

Genetic Variability and the Origin of House Mouse from the Territory of Russia and Neighboring Countries

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Abstract—Genetic differentiation and gene geographic variation of house mouse from the territory of Russia and neighboring countries was examined based on the allozyme analysis of samples from natural, semisynanthropic, and obligate synanthropic populations. The results of analysis of genetic differentiation, performed using 22 interpreted loci, as well as the data on gene geographic variation of four allozyme markers (*Idh-1*, *Sod-1*, *Aat-1*, and *hemoglobin*) validated the hypothesis on rapid mice expansion from the south of Eastern Europe to the Pacific coast of Asia. It was demonstrated that moving eastwards led to the formation currently expanding zones of hybridization between the “northern” *M. musculus* group and the “Central Asian” *M. wagneri* group in Siberia, and with the *M. m. castaneus* group in the south of the Russian Far East. The allozyme data were compared with the data of molecular genetic and karyological analyses performed using the same experimental material. The phenomenon of hybrid zones of the house mouse from Eurasia is discussed.

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INTRODUCTION

Analysis of biochemical variation in wild and synanthropic mouse populations of the subgenus *Mus*, started in the 1960s, had changed the concepts on the systematics of this taxon. The polytypic species of house mouse (*Mus musculus* L., 1758) [1] split into groups of related species or semispecies. In western Eurasia, sibling species of the subgenus *Mus* with sympatric and allopatric ranges were described [2–4].

The first stages of allozyme analysis of house mouse on the territory of the former Soviet Union mostly involved the population samples from southern and partly medium latitudes, from Moldova and the Ukraine to the Russian Far East, with natural biotopes suitable for the species habitation. At the southwest of former Soviet Union, in Transcaucasia, Moldova, and the Ukraine, sympatric habitation of one aboriginal species (either *M. macedonicus*, or *M. spicilegus*), and one synanthropic species (*M. musculus*) was described [5, 6]. Eastwards, in natural biotopes, as well as in the sites of semisynanthropic and obligate synanthropic habitation, only *M. musculus* s. str. was discovered [7]. It was demonstrated that on these territories, the genotypic population structure was substantially affected by the inhabitants of more southern regions of Asia. At the south of the Far East (Primorye), wide hybrid zone between *M. musculus* and the Southeast

Asia inhabitant, *M. m. castaneus*, was discovered. Determination of the borders of this zone requires analysis of additional material from earlier undiscovered regions of Siberia and the Far East.

The data on geographic distribution of the hemoglobin variants was found to be useful to describe the history of the house mouse dispersal throughout the world. It is known that electrophoretic hemoglobin haplotypes correspond to certain combinations of allelic variants of two consecutive globin beta loci (*b-1* and *b-2*) (Jahn et al., 1980; cited from [8]). Electrophoretic analysis of blood samples, hemolyzed with the help of distilled water (initial and most frequently used method), identified variation only at the *b-2* locus. This variation was represented by three haplotypes with differing minor zone characteristics, Hbb-s, Hbb-d, and the so-called “Asian” haplotype. Early studies of the hemoglobin variants geographic distribution showed that Hbb-d was distributed in the populations of house mouse throughout the world, excluding Central and North China (*M. m. gansuensis*), and the Korean Peninsula [9]. Close association between haplotype Hbb-s and the form *M. m. domesticus*, and between the “Asian” haplotype and the Central Asian forms of house mouse was demonstrated.

Treatment of the samples with iodine acetate [10] provided identification of electrophoretic differences

at the *b-1* and *b-2* loci. Specifically, the “Asian” haplotype split into two haplotypes, Hbb-p and Hbb-w1. Sequencing of the *b-1* and *b-2* loci showed that Hbb-p was a crossover form between haplotypes Hbb-d and Hbb-w1, and received the *b-1* allele from Hbb-d, and the *b-2* allele, from Hbb-w1 [8]. The hemoglobin haplotypes distribution patterns in Asian populations of house mouse [11] suggested that for a period of time the carriers of nonrecombinant haplotypes could evolve independently. This happened at the time when the carriers of haplotype Hbb-w1 populated Central Asia forming the range of aboriginal *wagneri* (probably, the member of special subspecies group within *M. musculus* [12]). During the presynanthropic period, the owners of haplotype Hbb-d occupied the southern part of Eurasia, and from there invaded the territory of Northern Asia. In this case, south of Eastern Europe could be the final region of presynanthropic invasion. However, at some evolutionary step, a partial overlap of the ranges of the forms discussed took place with the appearance of the individuals heterozygous for the loci of interest. Then, recombinant haplotype Hbb-p appeared. This haplotype in combination with the initial haplotype Hbb-w1 characterizes house mice from Central Asia and reflects progression of its genes in the populations from neighboring and remote territories. In other words, it seems likely that hemoglobin is a promising marker for tracing the migration pathways of the inhabitants of Northern Eurasia in the direction from south to north and from west to east.

D. Marshall [13] attributes the house mouse living eastwards of the Urals to the subspecies *M. m. wagneri*, thereby suggesting the colonization of trans-Ural territories of Russia by the mice coming from the Central Asian region. This means that the main direction of the dispersal was from south to north. The northeast of European Russia, Siberia (except the southernmost regions), and the Russian Far East are unsuitable for the year-round habitation of the house mouse in natural conditions [14]. These territories are predominantly populated by obligate synanthropic forms. According to V.A. Kucheruk [15], these territories were colonized by mice from southwestern Europe in the direction from west to east. Allelic markers of the three enzymes, *Idh-1*, *Sod-1*, and *Aat-1* can be considered as the markers of the opposite flow (from east to west). The meeting and crossing of the flows mentioned prepared the prerequisites to the formation of extended, complex hybrid zones.

Allozyme analysis carried out in the present study represents a part of the long-term complex genetic investigation of the house mouse. In addition to the allozyme analysis, this investigation, performed using the same samples, included the analysis of karyological data, as well as the characteristics of nuclear and mitochondrial DNA. Taken together, these data provide a new insight into the evolution and the history of the taxon dispersal, as well as the evaluation of modern

taxon composition. This was the long-term goal of our investigations.

The present study was focused on analysis of genetic differentiation and gene geographic variation of the house mouse from the territory of Russian and the countries, summarizing the data of allozyme analysis for the samples obtained from natural semisynanthropic, and obligate synanthropic populations.

MATERIALS AND METHODS

Experiments were performed using 867 animals caught in 108 localities in 1986 through 2000, in 2002, and in 2009. Summarized regional samples are demonstrated in the Table 1, and sampling localities are shown in Fig. 1.

Starch gel electrophoresis of the proteins was performed with subsequent histochemical staining of the gels for identification of 11 kidney enzymes and four blood proteins according to [16].

Genetic distances were calculated using the BIOSYS-1 software package [17]. Since comparison of rare allelic variants of some proteins, identified in the samples collected long ago, was impossible, quantitative variables of the genetic distances were calculated separately for the samples collected in 1987 through 1990, in 1991 through 1992, in 1993, 1994, 1996, 1997, 1998, 1999, and 2000. Each sample series contained geographically close, as well as spatially separated samples. The animals from the population of the city of Vladivostok were present in each sample series, enabling typing of the electrophoretic mobility variants of all main proteins in the samples taken in past time intervals.

Initially, electrophoretic analysis of hemoglobin was performed using hemolysates not treated with iodine acetate. Beginning from 1992, some samples, and from 1996, all samples were examined using untreated, as well as iodine acetate-treated hemolysates, making possible analysis of all samples in total.

RESULTS AND DISCUSSION

Electrophoretic analysis of eleven proteins, including lactate dehydrogenase (LDH), malate dehydrogenase (MOR), malic enzyme (MOD), isocitrate dehydrogenase (IDH), aspartate aminotransferase (AAT), superoxide dismutase (SOD), 6-phosphogluconate dehydrogenase (PGD), glucose-6-phosphate dehydrogenase (G6PD), sorbitol dehydrogenase (SDH), α -glycerophosphate dehydrogenase (α -GDH), and esterase (EST), hemoglobin (Hbb), and four plasma proteins made it possible to examine 22 interpretative loci.

Evaluation of the genetic distances showed that in *M. musculus* from the territory examined the values of population genetic differentiation were independent from the distances between the population localities. The UPGMA dendrogram (Fig. 2) was constructed based on the data obtained in 1987 through 1990. The

Table 1. Taxonomic composition, sampling regions, and sample sizes investigated

Region no.	Regions (numbers of sampling sites are on Fig. 1)	Differentiation over 22 loci		Geographic variation			
				Hbb (*including treated with iodine acetate.)		<i>Idh-1, Sod-1, Aat-1</i>	
		Years	Number of localities	Number of localities	Number of animals	Number of localities	Number of animals
<i>M. musculus</i>							
1	Moldova, Ukraine, and Moscow oblast (4–12)	1989–1990	3	9 3*	25 6*	9	23
2	Northern Caucasus (13)	1989	1	1	6	1	5
3	Volga region (14–17)	1998	3	4 3*	13 8*	4	12
4	Central Asia (18–27)	1989–1990	3	10	36	10	34
5	Southeastern Kazakhstan (28–33)	1989–1990 1996 2000	3 2 1	6 3*	37 17*	6	25
6	Western Siberia (34–38)	1989–1990 1992 1993 1996 1999 2000	1 1 1 1 1 2	5 4*	37 27*	5	34
7	Cis-Baikal region and Tuva (39–47)	1989–1990 2000	2 1	9 1*	39 6*	9	33
8	Transbaikalia (48–55)	1989–1990 1992 1998 1999	1 2 1 1	8 4*	72 49*	8	49
9	Yakutia (56–57)	1999	2	2*	5*	2	5
10	Cis-Amur region and marine coast of Khabarovsk krai (58–72)	1991–1992 1994 1996 1997 1998 2000	2 1 2 1 4 3	15 15*	116 97*	15	94
11	Northeast of Russia and Kamchatka Peninsula (73–75)	1992 1996 1999	1 1 1	3 3*	18 15*	3	17
12	Sakhalin and Kunashir islands (76–82)	1992 1993 1994 2000	2 2 1 2	7 4*	53 23*	7	48
13	Primorsky krai (83–108)	1989–1990 1991–1992 1994 1996 1997 1998 1999	4 4 2 2 4 3 2	25 14*	227 125*	25	262–197
<i>M. spicilegus</i>							
14	Moldova (1–3)	1989–1990	3 (30 animals)				

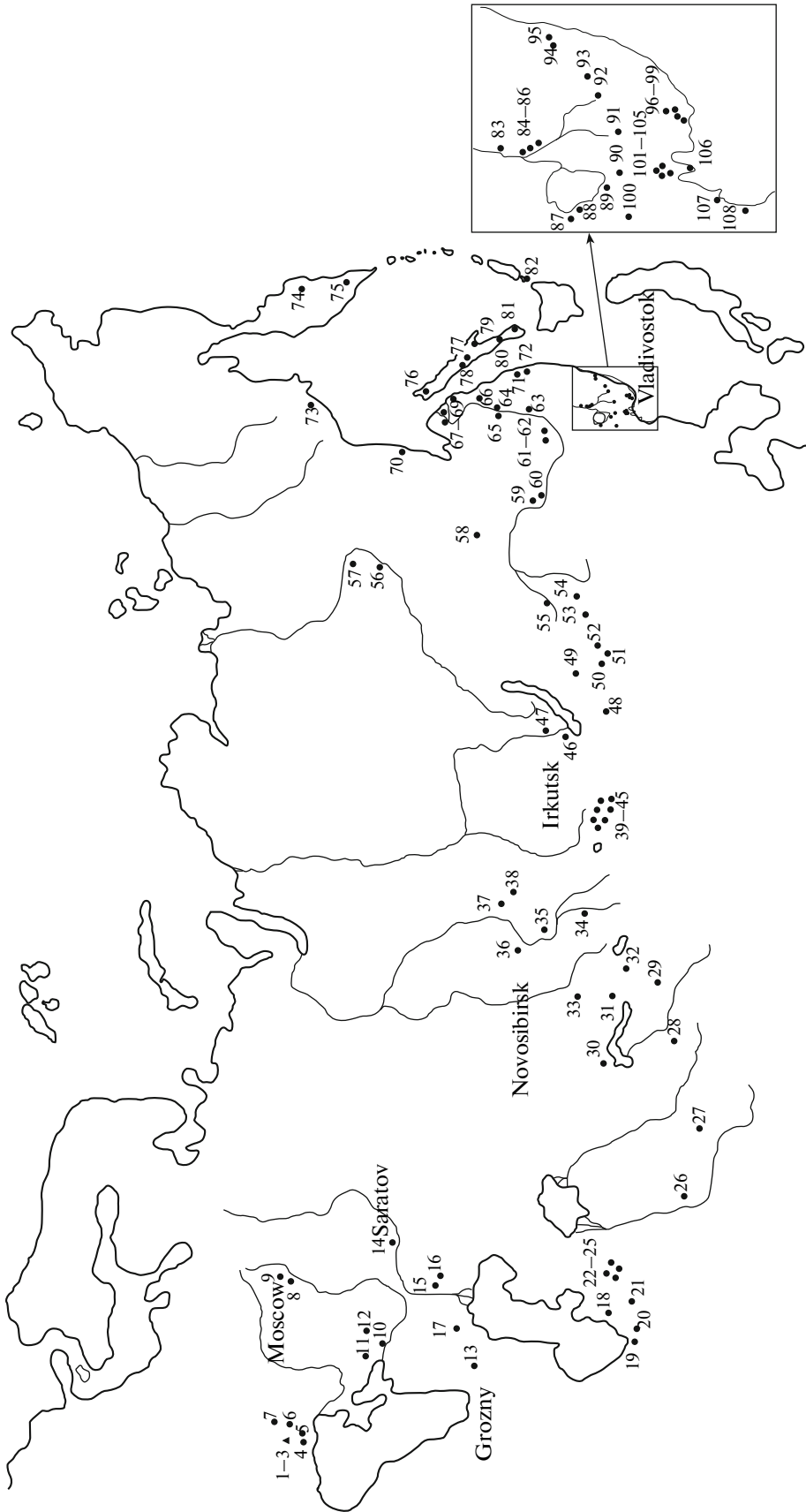


Fig. 1. Sampling localities.

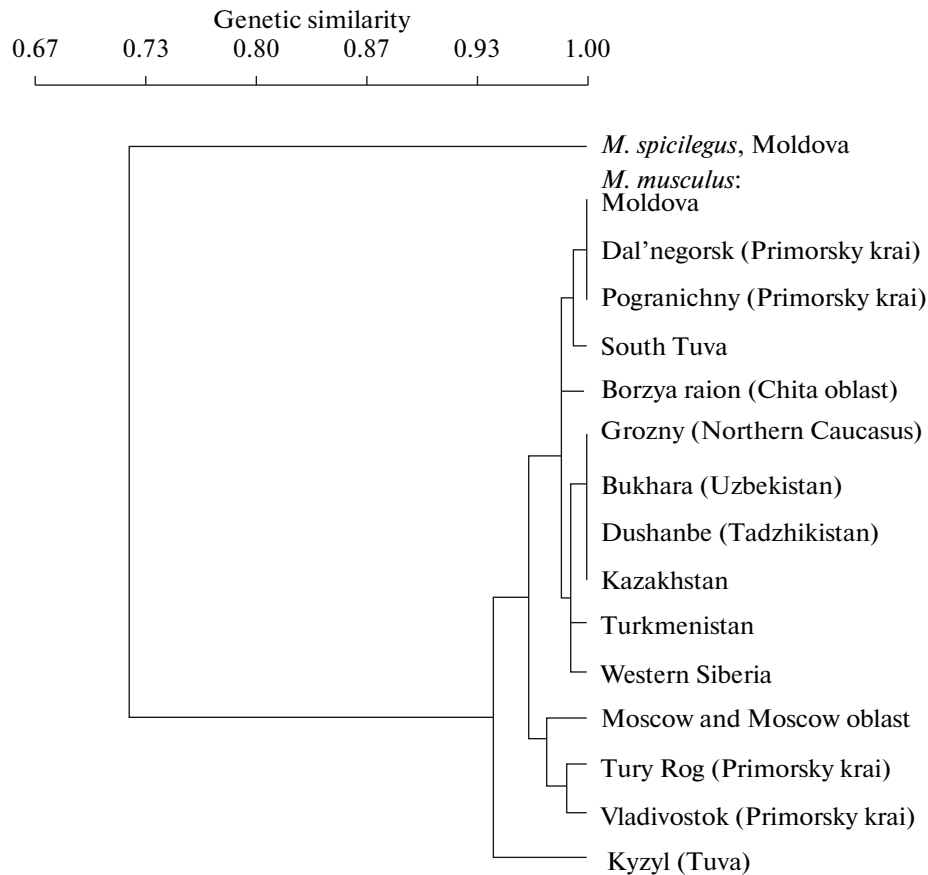


Fig. 2. UPGMA dendrogram of *Mus musculus* from Russia and neighboring countries.

dendrogram demonstrated substantial differences between *M. spicilegus* and *M. musculus*, pointing to high genetic similarity within the latter species, albeit giving no information on its intraspecific subdivision. Geographically distant samples could group in common clusters, while geographically close samples could be found in different clusters. Further investigations confirmed this conclusion. Zero values of Nei's unbiased genetic distances [18] were observed upon the pairwise comparison of rather geographically close populations: Khabarovsk–Blagoveshchensk; Inno- kent'evka (Primorsky krai)–Vanino (Khabarovsk krai), as well as upon comparison of spatially separated populations (Tomsk–Sakhalin; Tynda (Amur oblast)–Sakhalin). The highest genetic distance values (0.1 to 0.114) were found in the group of samples from Pri- morye (Vladivostok–Khasan), as well as upon the comparison of this and the other groups (Southeast Kazakhstan–Vladivostok; and Vladivostok–Komsol- sk-on-Amur).

Similarly to the data obtained at the first stage of investigation, UPGMA dendrograms constructed for each time interval, showed no dependence from the geographic distance between the populations. It seems likely that this is explained by rapid, passive expansion

across the vast territory from the western borders of the former Soviet Union to the Pacific coast of Asia.

Among 22 loci examined, polymorphism was not detected for *Ldh-1*, α -*Gpd*, and one protein from the total plasma proteins profile. Each of the *Ldh-5*, *Aat-2*, *Sod-2*, *Idh-2*, *Mor-1*, *Mor-2*, *Sdh*, *Alb*, and *Trf* was characterized by low geographic variation. In other words, the same major allele was represented in all samples.

Analysis of *Pgd*, *G6pd*, *Mor-1* and esterases in the samples of past years identified the variants with elec- trophoretic mobilities that we failed to compare. For four markers, *Idh-1*, *Sod-1*, *Aat-1*, and hemoglobin, generalization of the data for the whole period of investigation was possible, enabling investigation of gene geography in the populations of the house mouse from the territory of the former Soviet Union.

Isocitrate Dehydrogenase-1

In the samples of *M. musculus* distributed from the western borders of the former Soviet Union to the Pacific coast and the adjacent islands, four electro- phoretic variants of *Idh-1* were identified. One of these variants was identical to the *Idh-1-a-a* of *M. spicilegus*.

Table 2. Frequencies of the *Idh-1*, *Aat-1*, and *Sod-1* alleles in summarized regional samples of *Mus musculus*

Region no.	Regions	Number of localities	<i>Idh-1</i>				<i>Aat-1</i>		<i>Sod-1</i>		
			<i>a</i>	<i>b</i>	<i>n̄</i>	<i>d</i>	<i>a</i>	<i>b</i>	<i>a</i>	<i>b</i>	<i>0.5</i>
1	Moldova, Ukraine, and Moscow oblast	9		1			0.98	0.02		1	
2	Northern Caucasus	1		1			1			1	
3	Volga region	4		1			1			1	
4	Central Asia	10		1			1			0.99	0.01
5	Southeastern Kazakhstan	6		1			1			1	
6	Western Siberia	8	0.12	0.88			1			1	
7	Tuva Cis-Baikal region	8	0.03	0.88		0.09	1		0.11	0.89	
8	Transbaikalia	9	0.04	0.89		0.07	1			1	
9	Yakutia	2		1			0.9	0.1		1	
10	Cis-Amur region and marine coast of Khabarovsk krai	14	0.03	0.94		0.03	1		0.04	0.96	
11	Northeast of Russia and Kamchatka Peninsula	3	0.11	0.67	0.22		0.9	0.1	0.15	0.85	
12	Sakhalin and Kunashir islands, Yu.-Sakhalinsk	7	0.05	0.91	0.01	0.02	0.98	0.02	0.04	0.96	
		1	0.14	0.64	0.08	0.14					
13	Primorsky krai	25	0.23	0.64	0.12	0.01	0.76	0.24	0.13	0.87	

Another variant was marked relative to *M. musculus* from Moldova and *M. molossinus* from Japan as *Idh-1-b*. Since it was impossible to mark two more isocitrate dehydrogenase-1 variants identified in our samples, the pattern of their relative mobilities in Japan house mouse was used [19]. Compared to the *Idh-1-a-a*, the relative anodal mobility of *Idh-1-c-c* was 0.5. The *Idh-1-d-d* was a bit more anodal than *Idh-1-b-b*.

The *Idh-1-b* variant was distributed throughout the region examined. It was the only variant identified in the population samples from the European part of the former Soviet Union, as well as in the population samples from Asia and Kazakhstan (Table 2). The *Idh-1-a* is widespread in Primorye and is also found in other regions of the Far East and Siberia. The *Idh-1-d* as rare allele is present in the populations of Tuva, Transbaikalia, Sakhalin, and Primorye. Earlier, this allele was identified in the population of house mouse from Hokkaido Island [19].

The *Idh-1-c* variant, characteristic of *M. m. castaneus*, was detected in combination with *Idh-1-b* and *Idh-1-a* in the populations of house mouse from Primorsky krai and the large seaport towns of the Pacific coast of Russia, Yuzhno-Sakhalinsk, Magadan, and Petropavlovsk-Kamchatsky. The absence of *Idh-1-c*

from interior continental populations indicates that on the territory of Russia, *M. m. castaneus*, accompanying humans on the sea routes, moved northwards along the Pacific coast.

Aspartate Aminotransferase

In the material examined this enzyme was represented by two electrophoretic variants, *Aat-1-a* and *Aat-1-b*. Most of the house mouse population samples were monomorphic for *Aat-1-a*. In addition to Primorye, polymorphic populations were observed in Yakutia, at the south of Trans-Baikal krai, in Sakhalin, Magadan, and the neighboring continental coastline. The *Aat-1* biallelic polymorphism is characteristic of the populations of *M. m. castaneus* from Southeast Asia [20] and the northern part of Hindustan [21].

Superoxide Dismutase

Three electrophoretic variants were identified, including *Sod-1-b*, *Sod-1-a*, and *Sod-1-0.5*. The latter allele was detected in heterozygous phenotype *Sod-1-b-0.5* in one animal from Central Asia (Table 2). In most of the samples only *Sod-1-b* was detected. The

Sod-1-a was represented either as rare or additional allele in Tuvinian and Far Eastern populations of house mouse. According to the literature data, *Sod-1-a* is the major allele in *M. m. castaneus* [20].

The loci controlling the enzymes discussed are mapped to different chromosomes. Specifically, *Idh-1* is located on chromosome 1 [22], *Aat-1*, on chromosome 10 [23], and *Sod-1*, on chromosome 16 [24]. Nevertheless, each of these loci points to the invasion of the *M. m. castaneus* markers northwards along the Pacific coast, and further to the west.

A similar pattern can be inferred from the data on polymorphism of the mtDNA D loop hypervariable region. Using our collection of 1996–2000, samples representing 21 populations were randomly selected. In these samples, mice with the *M. m. castaneus* type of mtDNA were distributed only over the territory of the Far East (Primorye, Khabarovsk krai, Sakhalin, and Kamchatka) and Yakutia. These mice were not found in more western regions of Russia, as well as in Central Asia and Kazakhstan [25]. RAPD PCR analysis showed that *M. musculus* genotype was the background for all population [26]. The *M. m. castaneus* markers were mostly concentrated in the Far East region, in the populations of Primorye, Khabarovsk krai, and Sakhalin Island. The exclusion was the two animals from the obligate synanthropic population of the Olkhon Island (Lake Baikal). The patterns of geographic variation obtained reflected a relatively recent and still continuing period of the *M. m. castaneus* markers movement to the west.

Hemoglobin

Studying additional material mostly from the obligate synanthropic populations of Russia confirmed earlier obtained data [11] on geographic distribution of the hemoglobin haplotypes in Asian house mouse. In semisynanthropic and obligate synanthropic populations of house mouse from the European part of the former Soviet Union the major haplotype was Hbb-d (Table 3 and Figure 3). In most of the obligate synanthropic population samples from Asian part of Russia, this haplotype was also the major one, distinguishing these populations from the Central Asian semisynanthropic populations, haplotypes Hbb-p and Hbb-w1 prevailed. In case that iodine acetate treatment was not performed, in these populations, “Asian” haplotype was identified.

The observed pattern of the hemoglobin haplotypes geographic distribution pointed to the invasion of Central Asian haplotype Hbb-w1 and recombinant haplotype Hbb-p in the regions of Northern Asia and Eastern Europe. These haplotypes were found in the European part of the former Soviet Union, Yakutia, and in the Far East region, including the populations of Kamchatka and Sakhalin. Upon considerable prevalence of haplotype Hbb-d in obligate synanthropic populations, recombinant haplotype Hbb-p in these

populations was substantially more frequent compared to initial haplotype Hbb-w1. Note that the only animal, carrying another recombinant haplotype, Hbb-w2 was caught in Kazakhstan [27].

House mouse from the territory of Central Asia is generally characterized by the *M. m. musculus* type of mtDNA along with the presence of *M. m. bactiranus* markers [25]. Judging by karyological and morphological data, Turkmenia and Uzbekistan represent complex hybrid zones, which were formed with participation of *M. m. musculus*, *M. m. bactrianus*, and *M. m. wagneri* [12, 28]. Based on karyological data, Lower Volga Region is populated by *M. m. musculus*, *M. m. wagneri*, and their hybrids.

The reverse gene flow from northern obligate synanthropic form into southern semisynanthropic populations is also represented in the gene geography of hemoglobins. For instance, Hbb-d was detected in the population from Almaty (Kazakhstan), as well as in the samples from the Volga region and Central Asia. In these populations, the haplotype of interest is usually rare or additional. Another pattern was observed at the south of East Siberia. The mice inhabiting this region are morphologically close to the Central Asian *M. m. gansuensis*. In these populations, geographic distribution of haplotype Hbb-d was controversial. This haplotype was additional in the population from the south of Buryatia, being at the same time the major haplotype in the populations of Daurian steppe. The hemoglobin gene geography reflects secondary nature of the contact between semisynanthropic house mouse populations from Central Asia with obligate synanthropic inhabitants of more northern territories of Russia. At the same time, gene geographic patterns of Hbb, *Idh-1*, *Sod-1*, and *Aat*, indicated that Central Asian house mouse populations were similar to the mice from semisynanthropic populations of Eastern Europe. Genetic and morphological similarity of spatially separated populations can be explained by rapid mice expansion across the vast territory extending from Eastern Europe to the Pacific coast of Asia. Provided the directions of settlement in eastern European and Asian parts of Palearctic, gene geography of the hemoglobin *b-1* and *b-2* loci, *Idh-1*, *Sod-1*, and *Aat-1*, implies the movement of house mouse from west to the east, resulting in the contacts between the range of the “northern” *M. musculus* group and the “Central Asian” *M. m. wagneri* group in Siberia, and with range of *M. castaneus* at the south of the Russian Far East. Modern multidirectional migration flows of house mouse along various transportation corridors still have not yet smoothed out the differences between these groups.

The markers examined are specific to the nuclear genome, and as mentioned above, are independent from each other. Gene geography of each of the markers provides analysis of the superspecies history from the side of the individual gene (or haplotype), while examination of a set of five markers, including two

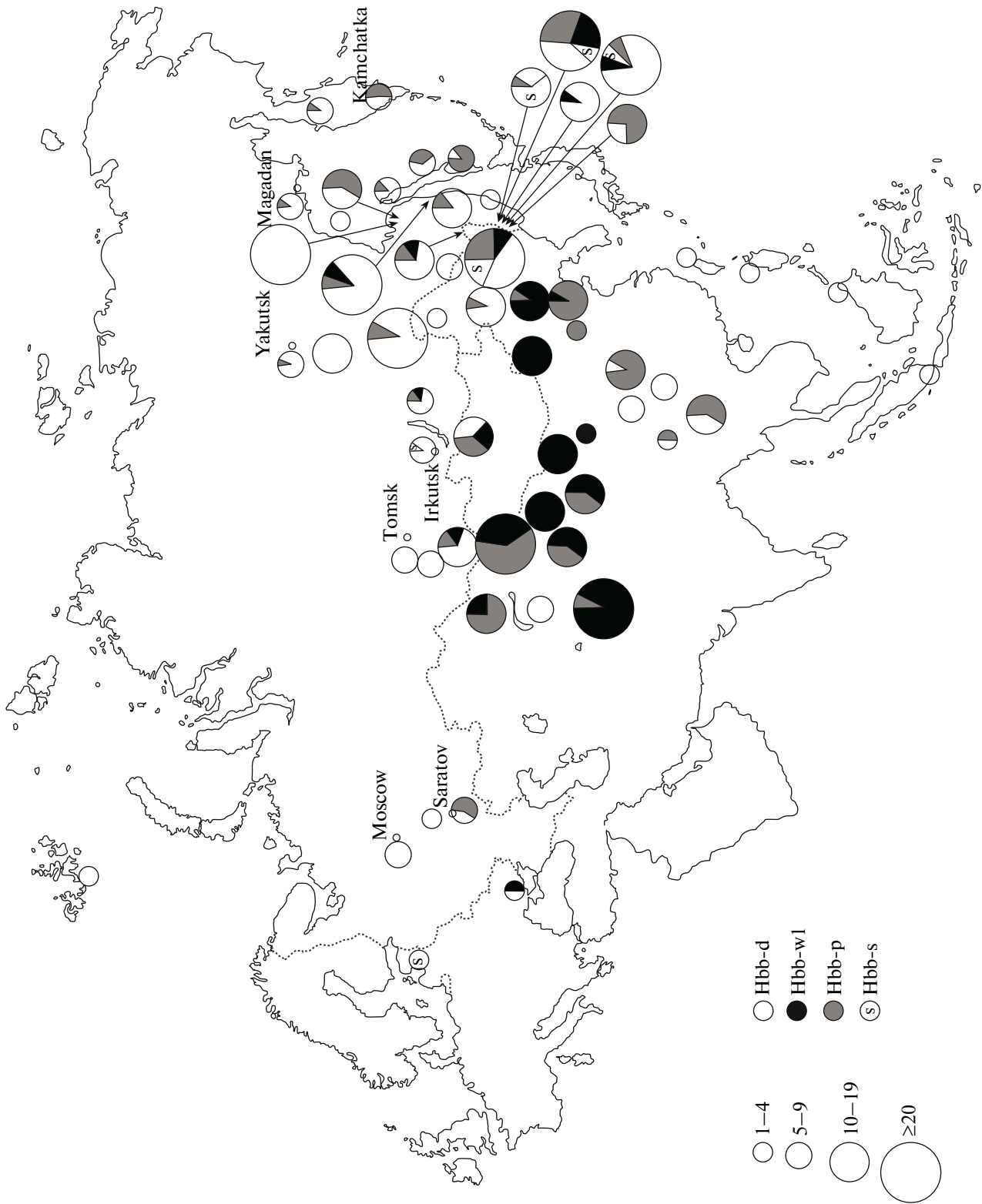


Fig. 3. Geographic distribution of hemoglobin haplotypes in *Mus musculus* from Eurasia (explicated from [11] with additions). Figures to the left of the circles, sample sizes.

Hbb loci, brings investigation to a new level, shedding a new light on the taxon evolution.

The gene pool of synanthropic house mice from the western part of Eurasia (semispecies *domesticus*) is distinguished for the wide distribution of the Hbb-c and Sod-1-a variants. The gene pool of the inhabitants of Southeast Asia (*castaneus*) is characterized by the presence of *Idh-1-c*, *Sod-1-a*, and the *Aat-1* biallelic polymorphism. The *Idh-1-b* and *Sod-1-b* characterize the gene pool of *M. m. musculus*. The prevalence of either *Hbb-d* or *Hbb-w1* haplotypes divides *M. m. musculus* into northern and Central Asian phyletic lineages. Nearly all of the variants mentioned are found in the populations from the southern foothills of the Himalayas. The gene geography of the five nuclear genome loci mentioned above confirms our earlier hypothesis on the common center of origin of the synanthropic forms of house mouse [7], limiting it to the southern regions of Asia. Analysis of nuclear genes [21, 29] pointed to extreme polymorphism of the populations from Indian subcontinent, with the presence of all alleles characterizing the populations of the range periphery, as well as the unique alleles. From here, southern foothills of the Himalayas can be with reasonable confidence considered as the start point of the house mouse dispersal. Similar data were obtained in analysis of mtDNA [30].

The presence of different sets of major alleles in the populations from the regions, peripheral to the center of dispersal (Europe–Northern Africa, northern Eurasia, Central Asia, and Southeast Asia), implies a rather long period of presynanthropic existence of these populations. This period was characterized by the formation of a circular range around the Tibetan Plateau and surrounding mountain ridges. This range was represented by the *castaneus* form in the south, Central Asian *musculus* and *wagneri–gansuensis* in the north and east, and *domesticus* in the west. There are no doubts that active, and later passive (associated with humans) dispersal of the mice provided contacts between the taxa ranges in the region of West Asia–Central Asia–Transcaucasia. High polymorphism of Transcaucasian populations described [31] confirms this proposal. Accompanying humans, house mouse have populated earlier inaccessible territories, including those located in the northern part of Eurasia.

Considering that there is close association between haplotype Hbb-s and *M. m. domesticus*, any case of the Hbb-s appearance outside of the semispecies range deserves special attention. Specifically, in Japan this haplotype was identified in two mice from Hokkaido, and on the southern island of Chichi-jima [20, 21]. The appearance of this variant in the samples of synanthropic house mice caught along the western border of the former Soviet Union can be coherently explained in terms of the gene “penetration” through the *M. m. musculus*–*M. m. domesticus* hybrid zone. Sporadic appearance of the variant of interest beyond the range of *M. m. domesticus* is usually treated as a

result of random drift. For instance, we found this variant in the house mouse samples from Kalmykia and Irkutsk. However, in the course of long-term investigation of the south of the Russian Far East, this haplotype was regularly detected, usually as a rare one, in the house mouse samples from different regions of Primorsky krai. At the same time, in mouse populations from the settlements of the southern Sikhote Alin (Chuguevka and Bulyga–Fadeevo), unlike the populations from other territories, this haplotype was found to be the major one. High concentration of Hbb-s was found in the house mouse samples from Northeastern China [11], where high occurrence of this haplotype, similarly to southern Sikhote Alin, awaits explanation.

The appearance of the *M. m. domesticus* features in the populations from Primorye was also detected using molecular genetic markers. The *M. m. domesticus*-typical mtDNA haplotypes were found in the suburbs of Valdivostok and Irkutsk [25]. According to RAPD data [26], the presence of *M. m. domesticus* can be found throughout Russia. Karyological evidence of the presence of the *M. m. domesticus* and (or) *M. m. castaneus* mice, carrying X-chromosome variant differing from *M. m. domestus*, in Siberia and the Far East was reported in many studies [12]. Since the animals examined could be the hybrids of other than the first generation, rather quaint combinations of morphological, karyological, and molecular (including biochemical) markers could be found in the hybrid genotypes.

The abundance and qualitative diversity of house mouse hybridization zones in Eurasia is surprising (Fig. 4). At the range junction of known forms, different hybridization zones were observed. These zones vary from narrow and stable ones with the elements of reproductive isolation, to vast and still changing their shapes. Moreover, sporadic appearance of the characteristics of one taxon within the range of another one far from their common borders was observed due to synanthropic “clotting” with single individuals.

The synanthropic step of the species history demonstrates active destruction of differentiation, earlier developed between the geographical groups of house mouse. The process of differentiation, which took place for several hundred thousand years, within the historically short period was replaced by dedifferentiation caused by hybridization. The data on the genetic basis of the elements of reproductive isolation existing between *M. m. domestics* and *M. m. musculus* [32], point to either polymorphic manifestation of this character in the populations [33], or to the polymorphism and recessive character [34]. It seems likely that these data evidence for the initial stages of the formation of reproductive isolation. On the other hand, synanthropic stage of the evolution of the taxon does not promote its positive termination.

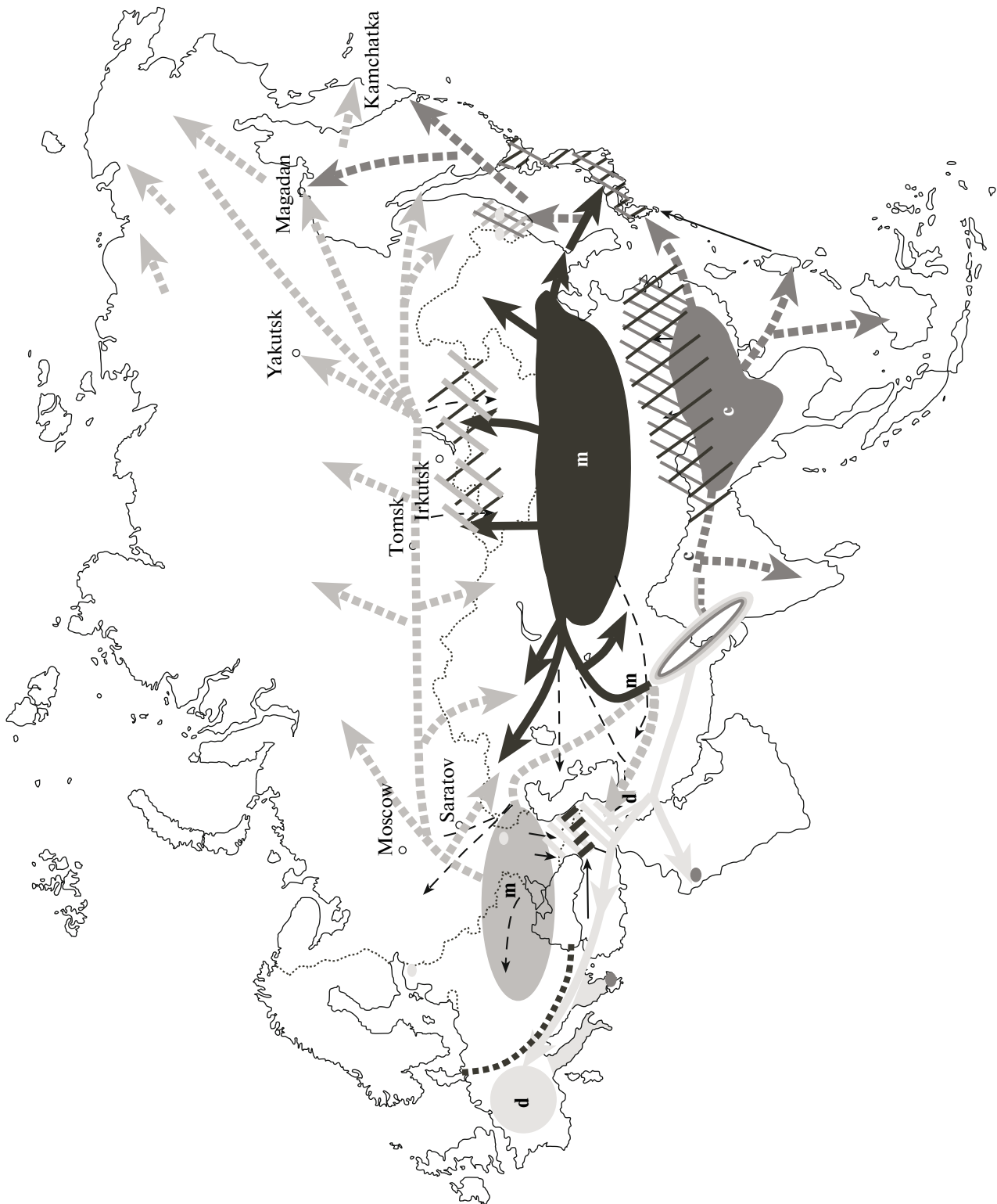


Fig. 4. Schematic depiction of the house mouse dispersal over the territory of Eurasia. m, *musculus*; c, *castaneus*; d, *domesticus*. The originally “northern” and Central Asian (“southern”) forms are shown by light and dark hatching, respectively.

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REFERENCES

- Schwarz, E. and Schwarz, H., The Wild and Commensal Stocks of the House Mouse *Mus musculus* Linnaeus, *J. Mammal.*, 1943, vol. 24, no. 1, pp. 59–72.
- Britton, J. and Thaler, L., Evidence for the Presence of Two Sympatric Species of Mice (Genus *Mus* L.) in Southern France Based on Biochemical Genetics, *Biochem. Genet.*, 1978, vol. 16, nos. 3–4, pp. 213–223.
- Darviche, D., Benmendi, F., Britton-Davidian, J., and Thaler, L., Note: Donnees preliminaires sur la systematique biochimique des genres *Mus* et *Apodemus* en Iran, *Mammalia*, 1979, vol. 43, no. 4, pp. 427–430.
- Thaler, L., Bonhomme, F., Britton-Davidian, J., and Hamar, M., The House Mouse Complex of Species: Sympatry of the House Mouse Biochemical Groups 2 and 4 in Rumania, *Zeitschrift Saugetierkunde*, 1981, vol. 46, pp. 169–173.
- Milishnikov, A.N., Lavrenchenko, L.A., Rafiev, A.N., and Orlov, V.N., About Biochemical and Morphological Identification of Some Forms of the Superspecies Complex *Mus musculus* s. lato, *Domovaya mysh'* (House Mouse), Kotenkova, E.V. and Bulatova, N.Sh., Eds., Moscow: Nauka, 1989., pp. 80–89.
- Mezhzherin, S.V. and Zagorodnyuk, I.V., Morphological, Karyological, and Genetic Differences between House *Mus musculus* and European Wild *Mus hortulanus* Mice, *Domovaya mysh'* (House Mouse), Kotenkova, E.V. and Bulatova, N.Sh., Eds., Moscow: Nauka, 1989, pp. 99–114.
- Frisman, L.V., Korobitsyna, K.V., Yakimenko, L.V., et al., Genetic Differentiation of House Mouse of the USSR Fauna: Electrophoretic Study of Proteins, *Biol. J. Linn. Soc.*, 1990, vol. 41, no. 1, pp. 65–72.
- Ueda, Y., Miyashita, N., Imai, K., et al., Nucleotide Sequences of the Mouse Globin Beta Gene cDNAs in a Wild Derived New Haplotype Hbb-wl, *Mammal. Genome*, 1999, vol. 10, no. 9, pp. 879–882.
- Miyashita, N., Moriwaki, K., and Minezawa, M., Allelic Constitution of the Hemoglobin Beta Chain in Wild Populations of the House Mouse *Mus musculus*, *Genetics*, 1985, vol. 23, no. 12, pp. 975–986.
- Petras, M. and Martin, J., Improved Electrophoretic Resolution of Some Hemoglobin Variants in *Mus musculus*, *Biochem. Genet.*, 1969, vol. 3, no. 3, pp. 303–309.
- Kawashima, T., Miyashita, K., Tsuchiya, K., et al., Geographical Distribution of the Hbb Haplotypes in the *Mus musculus* Subspecies in Eastern Asia, *Jpn. J. Genet.*, 1995, vol. 70, no. 1, pp. 17–23.
- Korobitsyna, K.V. and Yakimenko, L.V., The Role and Place of *wagneri*-Like Morphs of House Mouse (Rodentia: Muridae) in the Fauna of Russia and Adjacent Countries, *Zool. Zh.*, 2004, vol. 83, no. 8, pp. 1018–1030.
- Marshall, J., *Identification and Scientific Names of Eurasian House Mice and Their European Allies Subgenus Mus (Rodentia, Muridae)*, Springfield: Kinko's, 1826.
- Prilutskaya, L.I., Modern Geographic Range of House Mouse in the Soviet Union, *Domovaya mysh'* (House Mouse), Kotenkova, E.V. and Bulatova, N.Sh., Eds., Moscow: Nauka, 1989, pp. 15–27.
- Kucheruk, V.V., The Range of House Mice of the Superspecies Complex *Mus musculus* sensu lato, in *Domovaya mysh'* (*proiskhozhdenie, rasprostranenie, sistematika, povedenie*) (Origin, Distribution, Systematics, and Behavior of the House Mouse), Moscow: Nauka, 1994, pp. 56–80.
- Pasteur, N., Pasteur, G., Bonhomme, F., et al., *Practical Isozyme Genetics*, New York: Hebsted Press, 1988.
- Swofford, D.R. and Selander, R.B., Biosys-1: A FORTRAN Program for the Comprehensive Analysis of Electrophoretic Data in Population Genetic and Systematic, *J. Hered.*, 1981, vol. 72, no. 4, pp. 281–283.
- Nei, M., Estimation of Average Heterozygosity and Genetic Distance from a Small Number of Individuals, *Genetics*, 1978, vol. 89, pp. 583–590.
- Minezawa, M., Moriwaki, K., and Kondo, K., The Third Allele of Supernatant Isocitrate Dehydrogenase of House Mouse, Id-I-c, Originates from Asian Continent, *Jpn. J. Genet.*, 1980, vol. 55, no. 5, pp. 389–396.
- Bonhomme, F., Miyashita, N., Boursot, P., et al., Genetic Variation and Polyphyletic Origin in Japanese *Mus musculus*, *Heredity*, 1989, vol. 63, no. 3, pp. 299–308.
- Din, W., Anand, R., Boursot, P., et al., Origin and Radiation of the House Mouse: Clues from Nuclear Genes, *J. Evol. Biol.*, 1996, vol. 9, pp. 519–539.
- ICLAS Manual for Genetic Monitoring of Inbred Mice*, Tokyo: Univ. Tokyo Press, 1984.
- Creagan, R., Tishfield, J., McMorris, F.A., et al., Assignment of the Genes for Human Peptidase A to Chromosome 18 and Cytoplasmic Glutamic Oxaloacetate Transaminase to Chromosome 10 Using Somatic-Cell Hybrids, *Cytogenet. Cell Genet.*, 1973, vol. 12, no. 3, pp. 187–198.
- Francke, U. and Taggart, R., Regional Mapping of SOD-1 on Mouse Chromosome 16, and of HPRT and Alpha-Gal (Ags) on Mouse X, Using Chinese Hamster-Mouse T (X, 16) 16 H Somatic Cell Hybrids, *Cytogenet. Cell Genet.*, 1979, vol. 25, pp. 155–156.
- Yonekawa, H., Tsuda, K., and Yakimenko, L.V., et al., Genetic Diversity, Geographic Distribution and Evolutionary Relationships of *Mus musculus* Subspecies Based on Polymorphisms of Mitochondrial DNA, in *Problemy evolyutsii* (Problems of Evolution), Vladivostok: Dal'nauka, 2003, vol. 5, pp. 90–108.
- Spiridonova, L.N., Korobshchyna, K.V., Yakimenko, L.V., and Bogdanov, A.S., Genetic Diversity of the House Mouse *Mus musculus* and Geographic Distribution of Its Subspecies-Specific RAPD Markers on the Territory of Russia, *Russ. J. Genet.*, 2008, vol. 44, no. 5, pp. 584–594.
- Sato, J., Shinohara, A., Miyashita, N., et al., Discovery of a New Hbb Haplotype W2 in a Wild-Derived House Mouse, *Mus musculus*, *Mamm. Genome*, 2008, vol. 19, pp. 155–162.

28. Kozlovskii, A.I., Bulatova, N.Sh., and Orlov, V.N., Inconclusive Interpretations of the Results of Cytogenetic and Biochemical Analysis of House Mice from Turkmenistan, *Dokl. Akad. Nauk*, 1997, vol. 353, no. 3, pp. 165–169.
29. Awasihi, M., Bhat, K., and Anand, R., Genetic Heterogeneity in the Indian *Mus musculus*, *Biochem. Genet.*, 1998, vol. 36, no. 718, pp. 245–258.
30. Boursot, P., Din, W., Anand, R., et al., Origin and Radiation of the House Mouse: Mitochondrial DNA Phylogeny, *J. Evol. Biol.*, 1996, vol. 9, no. 4, pp. 391–415.
31. Milishnikov, A.N., Lavrepchenko, L.A., and Lebedev, V.S., Origin of the House Mice (Superspecies Complex *Mus musculus* sensu lato) from the Transcaucasia Region: A New Look at Dispersal Routes and Evolution, *Russ. J. Genet.*, 2004, vol. 40, no. 9, pp. 1011–1026.
32. Britton-Davidian, J., Fel-Clair, F., Lopez, J., et al., Postzygotic Isolation between the Two European Subspecies of the House Mouse: Estimates from Fertility Patterns in Wild and Laboratory-Bred Hybrids, *Biol. J. Linnean Soc.*, 2005, vol. 84, no. 3, pp. 379–393.
33. Vyskočilová, M., Pražanová, G., Forejt, J., and Pialek, J., Polymorphism in Hybrid Sterility Loci in Wild Derived *Mus m. musculus* Strains, in *Rodents et Spatium on Rodent Biology*, Proc. 11th Int. Conf., Myshkin, 2008, p. 11.
34. Oka, A., Aoto, T., Totsuka, Y., et al., Disruption of Genetic Interaction between Two Autosomal Regions and the X Chromosome Caused Reproductive Isolation between Mouse Strains Derived from Different Subspecies, *Genetics*, 2007, vol. 175, no. 2, pp. 185–197.